REMARKS

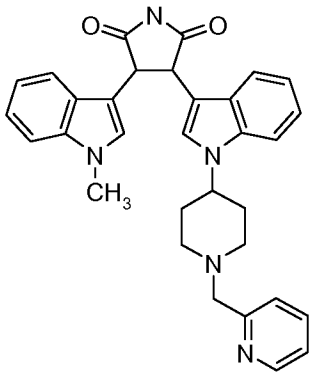
Claims 1-12 are pending in the present case, claims 13-20 are withdrawn, and claims 21-36 are cancelled. Claims 1-12 stand rejected under 35 USC 103(a) as being unpatentable over CAMERON et al. (WO 01/30331) in view of ROKHLIN et al. (J Biol Chem, 277:36, 33212-33219). In view of the reasons set forth below, it is submitted that the present rejection is improper and should be withdrawn. Reconsideration and reexamination of the present application in view of the amendments and remarks presented herein is respectfully requested.

Rejection under 35 USC 103(a)

CAMERON teaches generally that "isozyme selective inhibitors of protein kinase C," including a genus of bisindolmaleimides encompassing compounds of the present invention, "are useful in treating…cancer." (see p. 4, lines 6-12). Taken as a whole, CAMERON is primarily concerned with synergistic interactions between PKC inhibitors generally and other therapeutic agents (e.g., antioxidants, essentially fatty acids, or prostacyclin agents). CAMERON teaches neither the subgenus of the present case, nor use of any bisindolmaleimides to treat prostate cancer or androgen-independent prostatic adenocarcinoma.

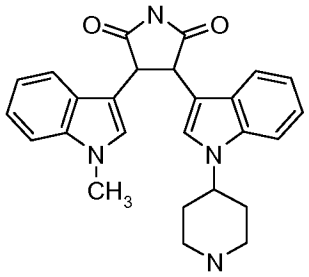
ROKHLIN investigated the effect of four bisindolmaleimide derivatives in human prostatic carcinoma cell lines and discovered that one of the four potentiates tumor necrosis factor (TNF) receptor family-mediated cell death substantially better than the other three. If anything, this suggests that biological activity among bisindolmaleimides is unpredictable, such that one of ordinary skill in the art would not be motivated to look for other compounds that were (1) less-related structurally than the three inferior compounds and (2) for which there was no demonstrated TNF activity. The compounds of Formula 1 fall into both these categories.

In further support of the unpredictability of compounds of this class, Applicants have surprisingly discovered that two structurally-related bisindolmaleimides disclosed in US 5,668,152 have different spectrums of biological activity.



LY317615 (reference compound)

See US 5,668,152 (see Example 49)



Compound 1 (representing compounds of Formula 1)

see US 5,668,152 (see Example 52)

Applicants assert that LY317615, also known as enzastaurin, is more closely-related structurally to the compounds of Formula 1 than the compounds cited in CAMERON and ROKHLIN. Applicant hereby informs the Examiner that enzastaurin is in phase 3 clinical trials for the treatment of nonhodgkin's lymphoma and that Compound 1 is a major metabolite of enzastaurin.

While both LY317615 and Compound 1 were previously described as being PKC-beta selective inhibitors, Applicant had discovered that Compound 1 also expresses substantial activity *via* the AKT pathway, while enzastaurin does not. (see attached 131 declaration by Applicant). Due to this dual mechanism, Applicants have now demonstrated that Compound 1 is substantially more effective, relative to LY317615, at treating tumors known to be treatable *via* the AKT pathway (e.g., prostate cancer, androgen-independent prostatic adenocarcinoma, glioblastoma, colon cancer, pancreatic cancer, ovarian cancer, endometrial cancer, and renal cell cancer). (for a description of tumors treatable via the AKT-pathway se, e.g., Hennesy et al, NATURE, v 4, pp. 988-1004 (December 2005)).

Taken together, CAMERON and ROKHLIN do not teach or suggest that the genus of compounds of the present invention have AKT activity or that they can be used to treated diseases known to be mediated through the AKT pathway. Further, given the unpredictability of the art demonstrated by ROKHLIN, one of ordinary skill in the art would not have been motivated to try the compounds of the present invention to treat the claimed diseases because they are too dissimilar in structure as compared to the TNF-active compounds tested of ROKHLIN. Finally, one of ordinary skill in the art would not have predicted that Compound 1 would show such superior results relative to enzastaurin in treating AKD-mediated cancers.

In view of the reasons set forth below, it is submitted that the present rejection is

improper and should be withdrawn. Reconsideration and reexamination of the present application in view of the amendments and remarks presented herein is respectfully requested.

Please charge any fees or credit any overpayment in connection with this application which may be required by this or any related paper to Deposit Account No. 05-0840.

If the Examiner has any questions, or would like to discuss any matters in connection with this application, he or she is invited to contact the undersigned at (317) 276-0307.

Respectfully submitted,

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ATTACHMENTS (3 Total)
131 declaration by Applicant
Table 1 (part of declaration)
Figures 1-2 (part of declaration)
Hennesy *et al* reference cited herein